Stem Cell Therapy: a Look at Current Research, Regulations, and Remaining Hurdles

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In September 2014, the Sanford Stem Cell Clinical Center at the University of California, San Diego (UCSD) Health System announced the launch of a groundbreaking clinical trial to assess the safety of neural stem cell–based therapy in patients with chronic spinal cord injury. Researchers hope that the transplanted stem cells will develop into new neurons that replace severed or lost nerve connections and restore at least some motor and sensory function.[1]

Two additional clinical trials at UCSD are testing stem cell–derived therapy for type-1 diabetes and chronic lymphocytic leukemia, the most common form of blood cancer.[1]

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These three studies are significant in that they are among the first efforts in stem cell research to make the leap from laboratory to human clinical trials. While the number of patients involved in each study is small, researchers are optimistic that as these trials progress and additional trials are launched, a greater number of patients will be enrolled. UCSD reports that trials for heart failure, amyotrophic lateral sclerosis, and blindness are in planning stages.[1]

The study of stem cells offers great promise for better understanding basic mechanisms of human development, as well as the hope of harnessing these cells to treat a wide range of diseases and conditions.[2] However, stem cell research—particularly human embryonic stem cell (hESC) research, which involves the destruction of days-old embryos—has also been a source of ongoing ethical, religious, and political controversy.[2]

The Politics of Progress

In 1973, the Department of Health, Education, and Welfare (now the Department of Health and Human Services) placed a moratorium on federally funded research using live human embryos.[3,4] In 1974, Congress adopted a similar moratorium, explicitly including in the ban embryos created through *in vitro* fertilization (IVF). In 1992, President George H.W. Bush vetoed legislation to lift the ban, and in 2001, President George W. Bush issued an executive order banning federal funding on stem cells created after that time.[3,4] Some states, however, have permitted their limited use. New Jersey, for example, allows the harvesting of stem cells from cloned human embryos, whereas several other states prohibit the creation or destruction of any human embryos for medical research.[3,4]

In 2009, shortly after taking office, President Barack Obama lifted the eight-year-old ban on federally funded stem cell research, allowing scientists to begin using existing stem cell lines produced from embryos left over after IVF procedures.[5] (A stem cell line is a group of identical stem cells that can be grown and multiplied indefinitely.)

The National Institutes of Health (NIH) Human Embryonic Stem Cell Registry[6] lists the hESCs eligible for use in NIH-funded research. At this writing, 283 eligible lines met the NIH's strict ethical guidelines for human stem cell research pertaining to the embryo donation process.[7] For instance, to get a human embryonic stem cell line approved, grant applicants must show that the embryos were "donated by individuals who sought reproductive treatment and who gave voluntary written consent for the human embryos to be used for research purposes."[8] The ESCs used in research are not derived from eggs fertilized in a woman's body.[9]

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Because of the separate legislative ban, it is still not possible for researchers to create new hESC lines from viable embryos using federal funds. Federal money may, however, be used to research lines that were derived using private or state sources of funding.[5]

While funding restrictions and political debates may have slowed the course of stem cell research in the United States,[10] the field continues to evolve. This is evidenced by the large number of studies published each year in scientific journals on a wide range of potential uses across a variety of therapeutic areas.[11–13]

The Food and Drug Administration (FDA) has approved numerous stem cell–based treatments for clinical trials. A 2013 report from the Pharmaceutical Research and Manufacturers of America lists 69 cell therapies as having clinical trials under review with the FDA, including 15 in phase 3 trials. The therapeutic categories represented in these trials include cardiovascular disease, skin diseases, cancer and related conditions, digestive disorders, transplantation, genetic disorders, musculoskeletal disorders, and eye conditions, among others.[14]

Still, the earliest stem cell therapies are likely years away. To date, the only stem cell–based treatment approved by the FDA for use in this country is for bone marrow transplantation.[15] As of 2010 (the latest year for which data are available), more than 17,000 blood cancer patients had had successful stem cell transplants.[16]

A Brief Stem Cell Timeline

Research on stem cells began in the late 19th century in Europe. German biologist Ernst Haeckel coined the term stem cell to describe the fertilized egg that becomes an organism.[17]

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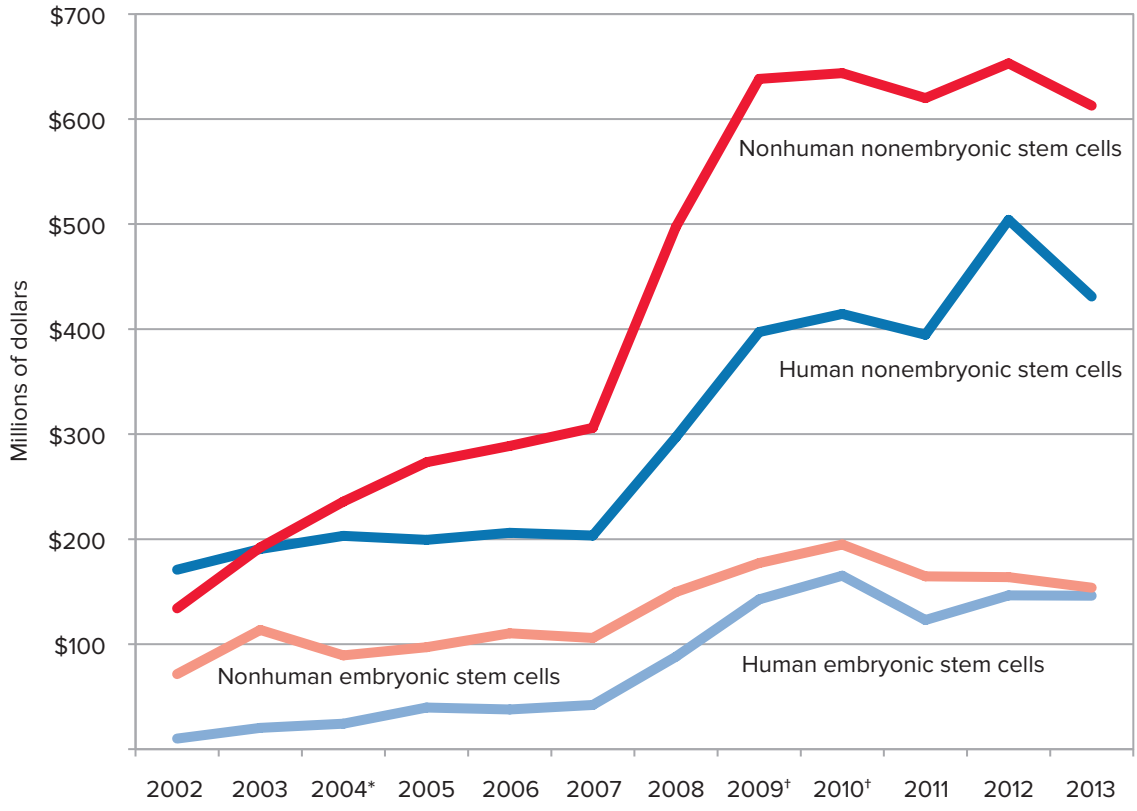
NIH Stem Cell Research Funding, Fiscal Years 2002–2013[47]



* Some institutes/centers changed their methodology for collecting nonhuman embryonic stem cell funding figures between FY 2003 and FY 2004, accounting for part of the funding drop in this category.

† Funding from the American Recovery & Reinvestment Act accounted for 15% of funding in both FY 2009 and FY 2010.

In the U.S., the study of adult stem cells took off in the 1950s when Leroy C. Stevens, a cancer researcher based in Bar Harbor, Maine, found large tumors in the scrotums of mice that contained mixtures of differentiated and undifferentiated cells, including hair, bone, intestinal, and blood tissue. Stevens and his team concluded that the cells were pluripotent, meaning they could differentiate into any cell found in a fully grown animal. Stem cell scientists are using that carefully documented research today.[17]

In 1968, Robert A. Good, MD, PhD, at the University of Minnesota, performed the first successful bone marrow transplant on a child suffering from an immune deficiency. Scientists subsequently discovered how to derive ESCs from mouse embryos and in 1998 developed a method to take stem cells from a human embryo and grow them in a laboratory.[17]

Why Stem Cells?

Many degenerative and currently untreatable diseases in humans arise from the loss or malfunction of specific cell types in the body.[9] While donated organs and tissues are often used to replace damaged or dysfunctional ones, the supply of donors does not meet the clinical demand.[18] Stem cells seemingly provide a renewable source of replacement cells and tissues for transplantation and the potential to treat a myriad of conditions.

Stem cells have two important and unique characteristics: First, they are unspecialized and capable of renewing themselves through cell division. When a stem cell divides, each new cell has the potential either to remain a stem cell or to differentiate into other kinds of cells that form the body's tissues and organs. Stem cells can theoretically divide without limit to replenish other cells that have been damaged.[9]

Second, under certain controlled conditions, stem cells can be induced to become tissue- or organ-specific cells with special functions. They can then be used to treat diseases affecting those specific organs and tissues. While bone marrow and gut stem cells divide continuously throughout life, stem cells in the pancreas and heart divide only under appropriate conditions.[9]

Embryonic Versus Adult Stem Cells

There are two main types of stem cells: 1) embryonic stem cells (ESCs), found in the embryo at very early stages of development; and 2) somatic or adult stem cells (ASCs), found in specific tissues throughout the body after development.[9]

The advantage of embryonic stem cells is that they are plu-

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ripotent—they can develop into any of the more than 200 cell types found in the body, providing the potential for a broad range of therapeutic applications. Adult stem cells, on the other hand, are thought to be limited to differentiating into different cell types of their tissue of origin.[9] Blood cells, for instance, which come from adult stem cells in the bone marrow, can specialize into red blood cells, but they will not become other cells, such as neurons or liver cells.

A significant advantage of adult stem cells is that they offer the potential for autologous stem cell donation. In autologous transplants, recipients receive their own stem cells, reducing the risk of immune rejection and complications. Additionally, ASCs are relatively free of the ethical issues associated with embryonic stem cells and have become widely used in research.

Induced Pluripotent Stem Cells

Representing a relatively new area of research, induced pluripotent stem cells (iPSCs) are adult stem cells that have been genetically reprogrammed back to an embryonic stem cell–like state. The reprogrammed cells function similarly to ESCs, with the ability to differentiate into any cell of the body and to create an unlimited source of cells. So iPSCs have significant implications for disease research and drug development.

Pioneered by Japanese researchers in 2006, iPSC technology involves forcing an adult cell, such as a skin, liver, or stomach cell, to express proteins that are essential to the embryonic stem cell identity. The iPSC technology not only bypasses the need for human embryos, avoiding ethical objections, but also allows for the generation of pluripotent cells that are genetically identical to the patient's. Like adult cells, these unlimited supplies of autologous cells could be used to generate transplants without the risk of immune rejection.[9]

In 2013, researchers at the Spanish National Cancer Research Centre in Madrid successfully reprogrammed adult cells in mice, creating stem cells that can grow into any tissue in the body. Prior to this study, iPSCs had never been grown outside Petri dishes in laboratories.[19] And, in July 2013, Japan's health minister approved the first use of iPSCs in human trials. The Riken Center for Developmental Biology will use the cells to attempt to treat age-related macular degeneration, a common cause of blindness in older people. The small-scale pilot study would test the safety of iPSCs transplanted into patients' eyes.[20]

The Promise of iPSCs

According to David Owens, PhD, Program Director of the Neuroscience Center at NIH's National Institute of Neurological Disorders and Stroke (NINDS), one of the fundamental hurdles to using stem cells to treat disease is that scientists do not yet fully understand the diseases themselves, that is, the genetic and molecular signals that direct the abnormal cell division and differentiation that cause a particular condition. "You want that before you propose a therapeutic," he says, "because you want a firm, rational basis for what you're trying to do, what you're trying to change."

Although most of the media attention around stem cells has focused on regenerative medicine and cell therapy, researchers are finding that iPSCs, in particular, hold significant promise as tools for disease modeling.[21,22] A major barrier to research is often inaccessibility of diseased tissue for study.[23] Because iPSCs can be derived directly from patients with a given disease, they display all of the molecular characteristics associated with the disease, thereby serving as useful models for the study of pathological mechanisms.

"The biggest payoff early on will be using these cells as a tool to understand the disease better," says Dr. Owens. For instance, he explains that creating dopamine neurons from iPSC lines could help scientists more closely study the mechanisms behind Parkinson's disease. "If we get a better handle on the disorders themselves, then that will also help us generate new therapeutic targets." Recent studies show the use of these patient-specific cells to model other neurodegenerative disorders, including Alzheimer's and Huntington's diseases.[24–26]

In addition to using iPSC technology, it is also possible to derive patient-specific stem cell lines using an approach called somatic cell nuclear transfer (SCNT). This process involves adding the nuclei of adult skin cells to unfertilized donor oocytes. As reported in spring 2014, a team of scientists from the New York Stem Cell Foundation Research Institute and Columbia University Medical Center used SCNT to create the first disease-specific embryonic stem cell line from a patient with type-1 diabetes. The insulin-producing cells have two sets of chromosomes (the normal number in humans) and could potentially be used to develop personalized cell therapies.[27]

Many Hurdles Ahead

The development of iPSCs and related technologies may help address the ethical concerns and open up new possibilities for studying and treating disease, but there are still barriers to overcome. One major obstacle is the tendency of iPSCs to form tumors *in vivo*. Using viruses to genomically alter the cells can trigger the expression of cancer-causing genes, or oncogenes.[28]

Much more research is needed to understand the full nature and potential of stem cells as future medical therapies. It is not known, for example, how many kinds of adult stem cells exist or how they evolve and are maintained.[9]

Some of the challenges are technical, Dr. Owens explains. For instance, generating large enough numbers of a cell type to provide the amounts needed for treatment is difficult. Some adult stem cells have a very limited ability to divide, making it difficult to multiply them in large numbers. Embryonic stem cells grow more quickly and easily in the laboratory. This is an important distinction because stem cell replacement therapies require large numbers of cells.[29]

Also, says Dr. Owens, stem cell transplants present immunological hurdles: "If you do introduce cells into a tissue, will they be rejected if they're not autologous cells? Or, you might have immunosuppression with the individual who received the cells, and then there are additional complications involved with that. That's still not entirely clear."

Such safety issues need to be addressed before any new stem cell–based therapy can advance to clinical trials with real patients. According to Dr. Owens, the preclinical testing stage typically takes about five years. This would include assessment of toxicity, tumorigenicity, and immunogenicity of the cells in treating animal models for disease.[30]

"Those are things we have to continually learn about and try to address. It will take time to understand them better," Dr. Owens says. Asked about the importance of collaboration in

overcoming the scientific, regulatory, and financial challenges that lie ahead, he says, "It's unlikely that one entity could do it all alone. Collaboration is essential."

Research and Clinical Trials

Ultimately, stem cells have huge therapeutic potential, and numerous studies are in progress at academic institutions and biotechnology companies around the country. Studies at the NIH span multiple disciplines, notes Dr. Owens, who oversees funding for stem cell research at NINDS. (Figure 1 shows the recent history of NIH funding for stem cell research.) He describes one area of considerable interest as the promotion of regeneration in the brain based on endogenous stem cells. Until recently, it was believed that adult brain cells could not be replaced. However, the discovery of neurogenesis in bird brains in the 1980s led to startling evidence of neural stem cells in the human brain, raising new possibilities for treating neurodegenerative disorders and spinal cord injuries.[31]

"It's a fascinating idea," says Dr. Owens. "It's unclear still what the functions of those cells are. They could probably play different roles in different species, but just the fundamental properties themselves are very interesting." He cites a number of NINDS-funded studies looking at those basic properties.

In another NIH-funded study, Advanced Cell Technology (ACT), a Massachusetts-based biotechnology company, is testing the safety of hESC-derived retinal cells to treat patients with an eye disease called Stargardt's macular dystrophy. A second ACT trial is testing the safety of hESC-derived retinal cells to treat age-related macular degeneration patients.[32,33]

In April 2014, scientists at the University of Washington reported that they had successfully regenerated damaged heart muscles in monkeys using heart cells created from hESCs. The research, published in the journal *Nature*, was the first to show that hESCs can fully integrate into normal heart tissue.[34]

The study did not answer every question and had its complications—it failed to show whether the transplanted cells improved the function of the monkeys' hearts, and some of the monkeys developed arrhythmias.[34,35] Still, the researchers are optimistic that it will pave the way for a human trial before the end of the decade and lead to significant advances in treating heart disease.[29]

In May 2014, Asterias Biotherapeutics, a California-based biotechnology company focused on regenerative medicine, announced the results of a phase 1 clinical trial assessing the safety of its product AST-OPC1 in patients with spinal cord injuries.[36] The study represents the first-in-human trial of a cell therapy derived from hESCs. Results show that all five subjects have had no serious adverse events associated with the administration of the cells, with the AST-OPC1 itself, or with the immunosuppressive regimen. A phase 1/2a dose-escalation study of AST-OPC1 in patients with spinal cord injuries is awaiting approval from the FDA.[37]

The FDA itself has a team of scientists studying the potential of mesenchymal stem cells (MSCs), adult stem cells traditionally found in the bone marrow. Multipotent stem cells, MSCs differentiate to form cartilage, bone, and fat and could be used to repair, replace, restore, or regenerate cells, including those needed for heart and bone repair.[38]

Publicly available information about federally and privately funded clinical research studies involving stem cells can be found at http://clinicaltrials.gov. However, the FDA cautions that the information provided on that site is supplied by the product sponsors and is not reviewed or confirmed by the agency.

"The biggest payoff early on will be using these cells as a tool to understand the disease better. If we get a better handle on the disorders themselves, then that will also help us generate new therapeutic targets."

—David Owens, PhD, Program Director, Neuroscience Center, National Institute of Neurological Disorders and Stroke

Global Research Efforts

Stem cell research policy varies significantly throughout the world as countries grapple with the scientific and social implications. In the European Union, for instance, stem cell research using the human embryo is permitted in Belgium, Britain, Denmark, Finland, Greece, the Netherlands, and Sweden; however, it is illegal in Austria, Germany, Ireland, Italy, and Portugal.[39]

In those countries where cell lines are accessible, research continues to create an array of scientific advances and widen the scope of stem cell application in human diseases, disorders, and injuries. For example, in February 2014, Cellular Biomedicine Group, a China-based company, released the six-month follow-up data analysis of its phase 1/2a clinical trial for ReJoin, a human adipose-derived mesenchymal precursor cell (haMPC) therapy for knee osteoarthritis. The study, which tested the safety and efficacy of intra-articular injections of autologous haMPCs to reduce inflammation and repair damaged joint cartilage, showed knee pain was significantly reduced and knee mobility was improved.[40] And the journal *Stem Cell Research & Therapy* reported that researchers at the University of Adelaide in Australia recently completed a project showing stem cells taken from teeth could form "complex networks of brain-like cells." Although the cells did not grow into full neurons, the researchers say that it will happen given time and the right conditions.[41]

The Regulation of Stem Cells

In February 2014, the U.S. Court of Appeals for the District of Columbia Circuit upheld a 2012 ruling that a patient's stem cells for therapeutic use fall under the aegis of the FDA.[42] The appeals case involved the company Regenerative Sciences, which was using patients' MSCs in its Regenexx procedure to treat orthopedic problems.[43]

The FDA's Center for Biologics Evaluation and Research (CBER) regulates human cells, tissues, and cellular and tissue-

based products (HCT/P) intended for implantation, transplantation, infusion, or transfer into a human recipient, including hematopoietic stem cells. Under the authority of Section 361 of the Public Health Service Act, the FDA has established regulations for all HCT/Ps to prevent the transmission of communicable diseases.[44]

The Regenexx case highlights an ongoing debate about whether autologous MSCs are biological drugs subject to FDA approval or simply human cellular and tissue products. Some medical centers collect, concentrate, and reinject MSCs into a patient to treat osteoarthritis but do not add other agents to the injection. The FDA contends that any process that includes culturing, expansion, and added growth factors or antibiotics requires regulation because the process constitutes significant manipulation. Regenerexx has countered that the process does not involve the development of a new drug, which could be given to a number of patients, but rather a patient's own MSCs, which affects just that one patient.

Ensuring the safety and efficacy of stem cell–based products is a major challenge, says the FDA. Cells manufactured in large quantities outside their natural environment in the human body can potentially become ineffective or dangerous and produce significant adverse effects such as tumors, severe immune reactions, or growth of unwanted tissue. Even stem cells isolated from a person's own tissue can potentially present these risks when put into an area of the body where they could not perform the same biological function that they were originally performing. Stem cells are immensely complex, the FDA cautions—far more so than many other FDA-regulated products—and they bring with them unique considerations for meeting regulatory standards.

To date, no U.S. companies have received FDA approval for any autologous MSC therapy, although a study is ongoing to assess the feasibility and safety of autologous MSCs for osteoarthritis.[45] One of the major risks with MSCs is that they could potentially lead to cancer or differentiation into bone or cartilage.[46]

What's Next

The numerous stem cell studies in progress across the globe are only a first step on the long road toward eventual therapies for degenerative and life-ending diseases. Because of their unlimited ability to self-renew and to differentiate, embryonic stem cells remain, theoretically, a potential source for regenerative medicine and tissue replacement after injury or disease. However, the difficulty of producing large quantities of stem cells and their tendency to form tumors when transplanted are just a few of the formidable hurdles that researchers still face. In the meantime, the shorter-term payoff of using these cells as a tool to better understand diseases has significant implications.

Social and ethical issues around the use of embryonic stem cells must also be addressed. Many nations, including the U.S., have government-imposed restrictions on either embryonic stem cell research or the production of new embryonic stem cell lines. Induced pluripotent stem cells offer new opportunities for development of cell-based therapies while also providing a way around the ethical dilemma of using embryos, but just how good an alternative they are to embryonic cells remains to be seen.

It is clear that many challenges must be overcome before stem cells can be safely, effectively, and routinely used in the clinical setting. However, their potential benefits are numerous and hold tremendous promise for an array of new therapies and treatments.

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